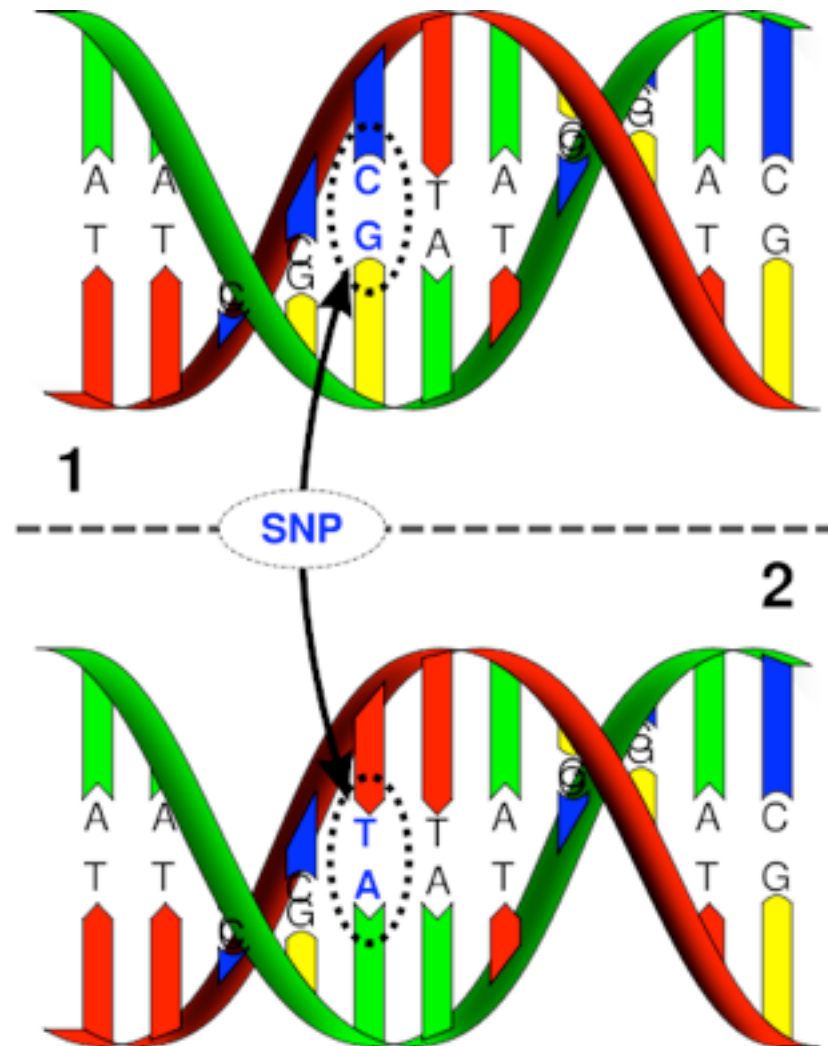


Single Nucleotide Polymorphisms (SNPs)



Sequence variations

- Single nucleotide polymorphisms
- Insertions/deletions
- Copy number variations (large: > 1 kb)
- Variable (short) number tandem repeats

Single Nucleotide Polymorphisms (SNPs)

- A single nucleotide (A,T,C,G) DNA sequence alteration
 - ... **A****C**GGCTAA ...
 - ... **A****T**GGCTAA ...
- It must occur in at least 1% of the population
- ~30 million SNPs
- SNPs make up ~80-90% of all human genetic variations
- Occur every 100-300 bases along the 3-billion-base human genome
- Evolutionary stable

dbSNP

- rs numbers
- chromosome and positions (ncbi36 vs GRCh37)

Reference SNP(refSNP) Cluster Report: rs17822931 **clinically associated**

http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=17822931

NCBI Single Nucleotide Polymorphism

PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM Books SNP

Search for SNP on NCBI Reference Assembly

Search Entrez SNP for Go

BUILD 132
Have a question about dbSNP? Try searching the SNP FAQ Archive!

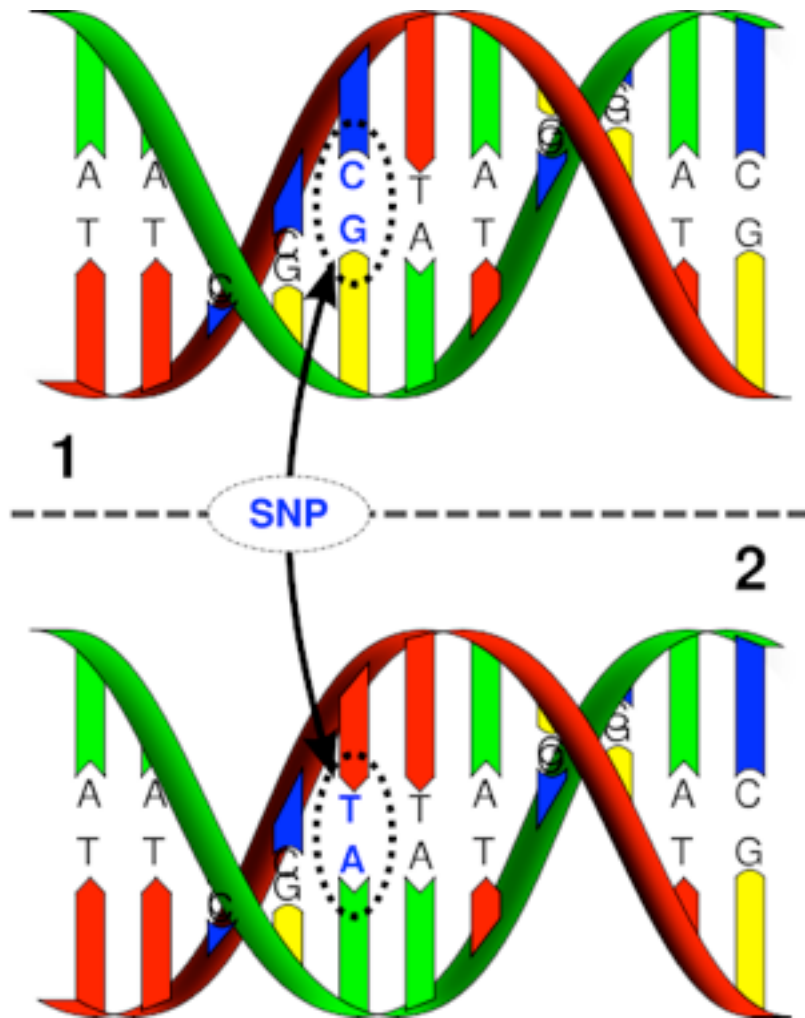
GENERAL
HUMAN VARIATION
Search, Annotate, Submit **NEW**
Annotate and Submit Batch Data with Clinical Impact **NEW**

Reference SNP(refSNP) Cluster Report: rs17822931 **clinically associated**

RefSNP	Allele
Organism: human (Homo sapiens)	Variation Class: SNP: single nucleotide polymorphism
Molecule Type: Genomic	RefSNP Alleles: A/C/G/T
Created/Updated in build: 123/132	Ancestral Allele: G
Map to Genome Build: 37.1	Clinical Association: VarView OMIM
Citation: PubMed	

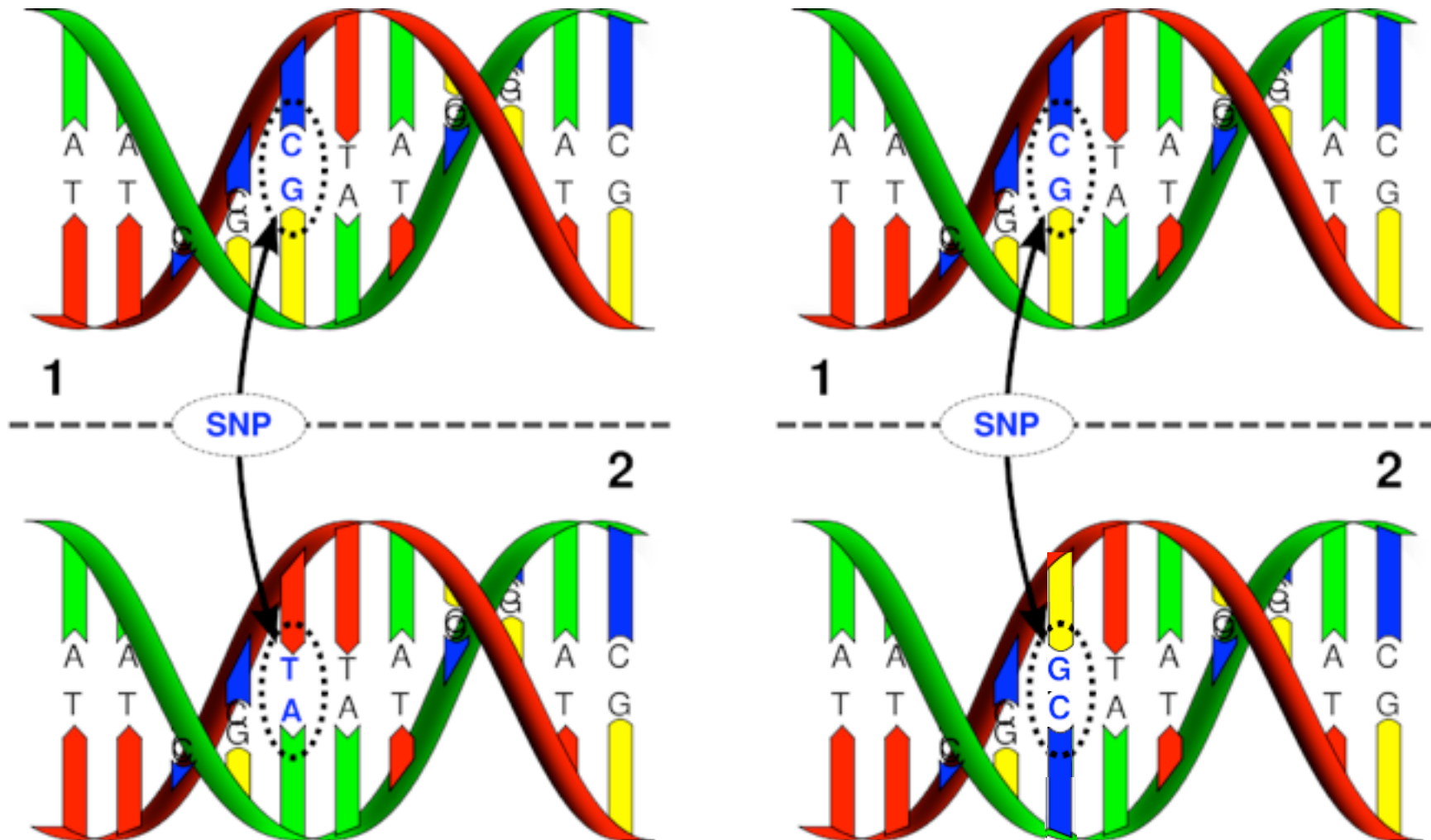
Strand issues

Importance of noting whether a SNP is mapped to forward or reverse strand



Strand issues

Importance of noting whether a SNP is mapped to forward or reverse strand



SNP arrays

Affymetrix SNP 6.0

Affymetrix SNP 5.0

Affymetrix GeneChip Human Mapping 250K

Affymetrix Axiom GW

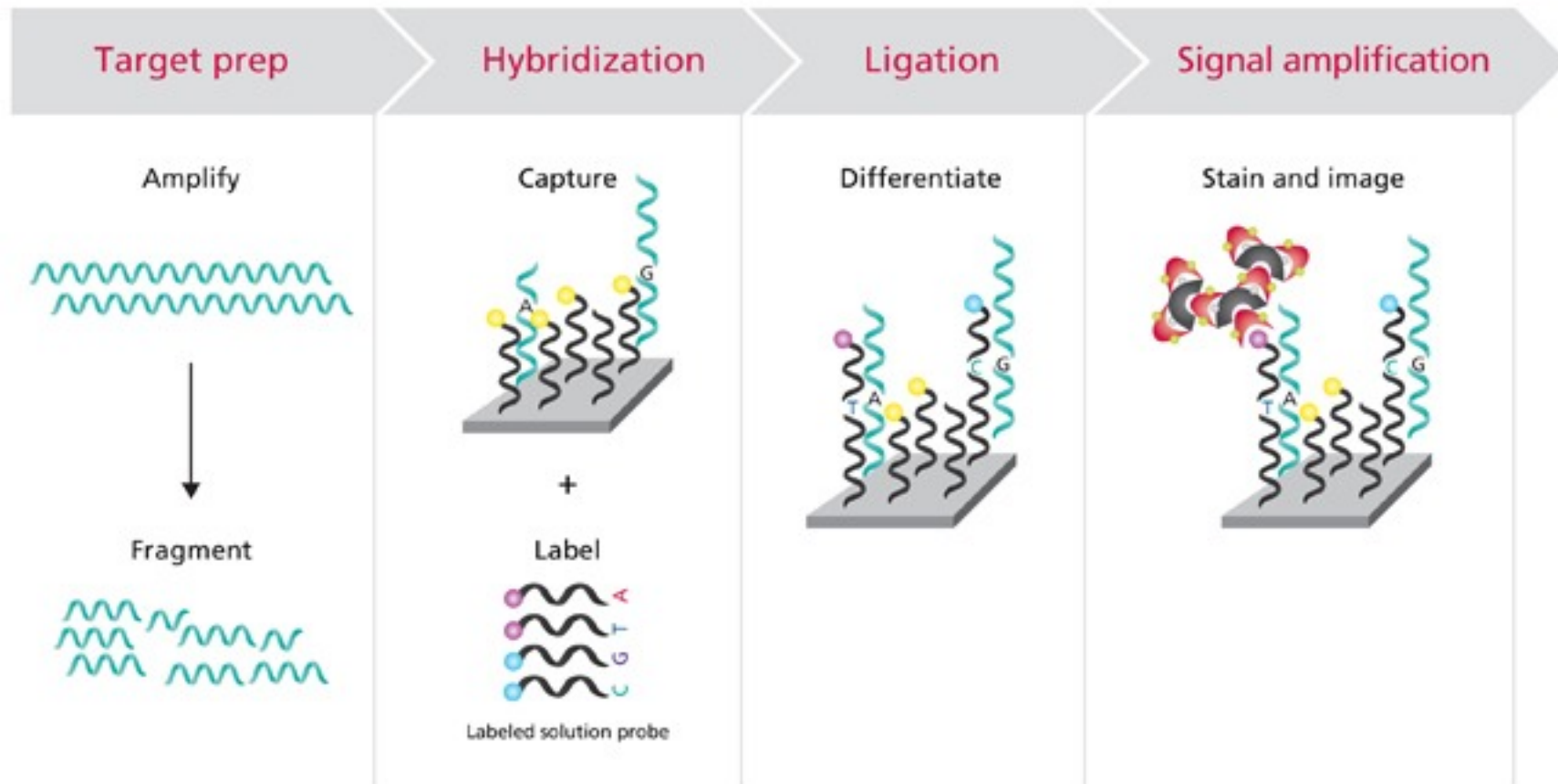
Illumina Human Hap 650v3

Illumina Human Hap 550v3

Illumina Human Hap 300v3



SNP arrays



Genome-wide association studies

Cases vs controls

- Obtain DNA from a disease group (e.g. asthma) and a control group
- For each individual: Run DNA on a SNP array measuring the genotypes at almost 1M loci
- If the group consists of 1,000 individuals, one obtains 1,000 x 1,000,000 genotypes
- Quality Control
- Loop over all SNPs, and identify those that are significantly more common among cases than controls
- Those SNPs are associated with the disease (in this study)
- Not necessarily causal

GWAS tools

PLINK

<http://pngu.mgh.harvard.edu/~purcell/plink/>

SNPTTEST

<http://www.stats.ox.ac.uk/~marchini/software/gwas/snptest.html>

Quality control

- Allele, genotypes frequencies, HWWE tests
- Missing genotype rates
- Inbreeding, IBS and IBD statistics for individuals and pairs of individuals
- non-Mendelian transmission in family data
- Sex checks based on X chromosome SNPs
- Tests of non-random genotyping failure
- Ethnicity

HapMap

- CEU
- CHB
- JPT
- YRI
- ...

HapMap Sample Populations

http://hapmap.ncbi.nlm.nih.gov/hapmappopulations.html.en

International HapMap Project

Home | About the Project | Data | Publications | Tutorial

中文 | [English](#) | Français | 日本語 | Yoruba

About the HapMap

- What is the HapMap?
- Origins of Haplotypes
- Health Benefits
- Populations Sampled
- Ethical Issues
- Consent Forms
- Community Advisory Groups(CAG)
- Data Release Policy
- Guidelines For Data Use
- Guidelines For Referring to HapMap Populations

Project Information

- About the Project
- HapMap Publications
- HapMap Tutorial
- HapMap Mailing List
- HapMap Project Participants

Useful Links

- HapMap Project Press Release
- NHGRI HapMap Page
- NHGRI Variation Database (dbSNP)

Which Populations Are Being Sampled

The International HapMap Project is analyzing DNA from populations with African, Asian, and European ancestry. Together, these DNA samples should enable HapMap researchers to identify most of the common haplotypes that exist in populations worldwide. [[See What Is the HapMap?](#)]

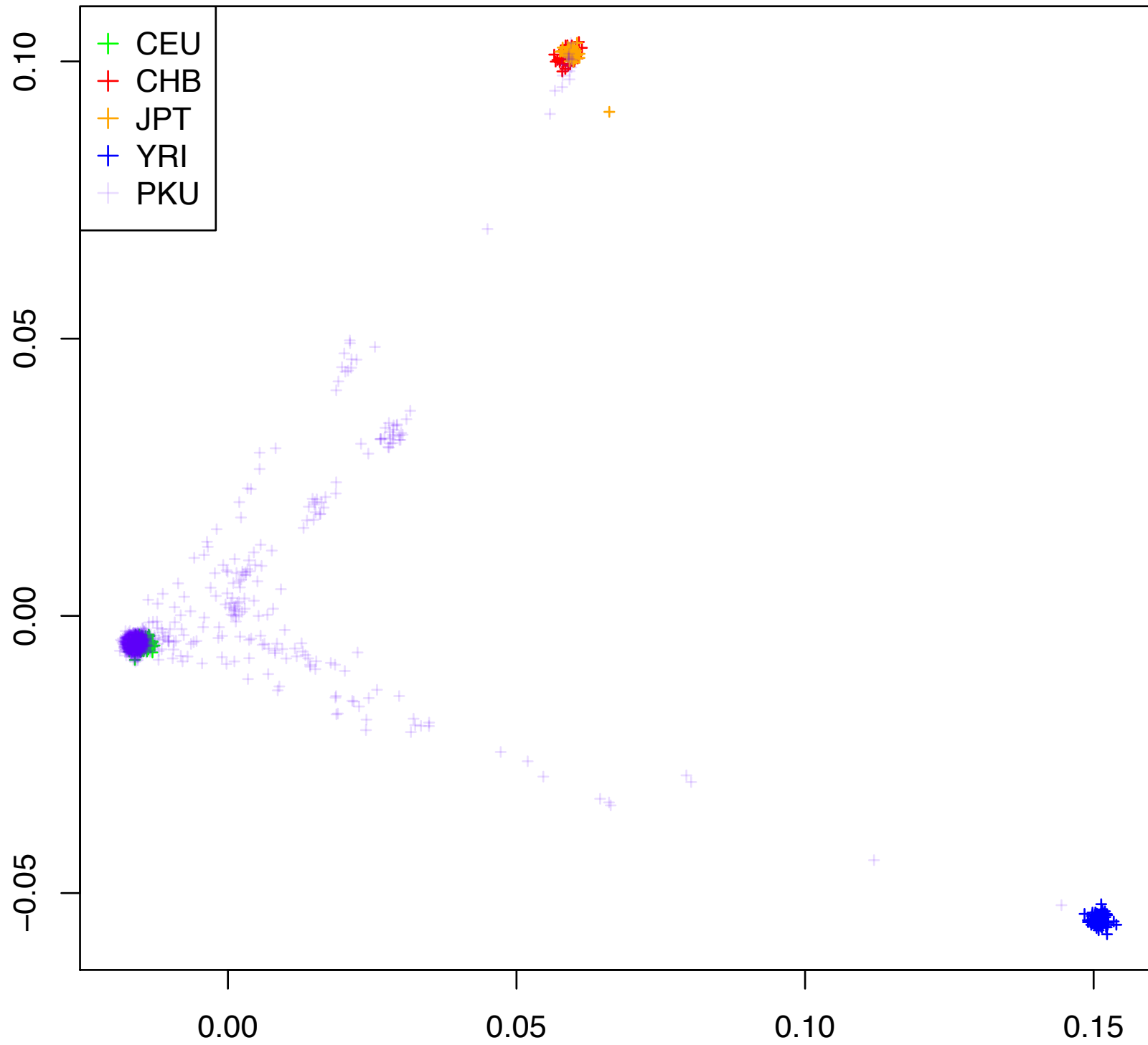
Because of the history of the human species, most of the common haplotypes in human chromosomes occur in all human populations. [[See The Origin of Haplotypes.](#)] However, any given haplotype may be more common in one population and less common in another, and newer haplotypes may be found in just a single population. Efficiently choosing the tag SNPs needed to identify haplotypes therefore requires looking at haplotype frequencies in multiple populations. Also, genetic data from more than one population will enhance the ability of researchers to study the genetic contributions to diseases that are more or less prevalent in different groups.

The DNA samples for the HapMap have come from a total of 270 people. The Yoruba people of Ibadan, Nigeria, provided 30 sets of samples from two parents and an adult child (each such set is called a trio). In Japan, 45 unrelated individuals from the Tokyo area provided samples. In China, 45 unrelated individuals from Beijing provided samples. Thirty U.S. trios provided samples, which were collected in 1980 from U.S. residents with northern and western European ancestry by the Centre d'Etude du Polymorphisme Humain (CEPH).

The blood samples are being converted into cell lines, which are used to make DNA, by the non-profit [Coriell Institute for Medical Research](#). Coriell provides DNA and cell lines from the samples for research projects that have been approved by the appropriate ethics committees. The samples and cell lines are not linked to any individual in the populations studied. However, the samples and cell lines are identified as coming from one of the four populations participating in the study, which raises ethical issues associated with conducting genetic research in named populations. [[See How Are Ethical Issues Being Addressed?](#) and [Guidelines for Referring to the HapMap Populations in Publications and Presentations.](#)]

To assess how much additional information would be gained by genotyping other populations, haplotypes in a set of chromosomal regions are being analyzed in samples from several additional populations.

PCA plot: patients vs HapMap



ARTICLE

NordicDB: a Nordic pool and portal for genome-wide control data

Monica Leu^{*,1,2}, Keith Humphreys¹, Ida Surakka^{2,3}, Emil Rehnberg¹, Juha Muilu², Päivi Rosenström², Peter Almgren⁴, Juha Jääskeläinen⁵, Richard P Lifton⁶, Kirsten Ohm Kyvik⁷, Jaakko Kaprio^{2,8,9}, Nancy L Pedersen¹, Aarno Palotie^{2,10,11}, Per Hall¹, Henrik Grönberg¹, Leif Groop⁴, Leena Peltonen^{2,3,10,11}, Juni Palmgren^{1,12} and Samuli Ripatti^{*,2,3}

A cost-efficient way to increase power in a genetic association study is to pool controls from different sources. The genotyping effort can then be directed to large case series. The Nordic Control database, NordicDB, has been set up as a unique resource in the Nordic area and the data are available for authorized users through the web portal (<http://www.nordicdb.org>). The current version of NordicDB pools together high-density genome-wide SNP information from ~5000 controls originating from Finnish, Swedish and Danish studies and shows country-specific allele frequencies for SNP markers. The genetic homogeneity of the samples was investigated using multidimensional scaling (MDS) analysis and pairwise allele frequency differences between the studies. The plot of the first two MDS components showed excellent resemblance to the geographical placement of the samples, with a clear NW–SE gradient. We advise researchers to assess the impact of population structure when incorporating NordicDB controls in association studies. This harmonized Nordic database presents a unique genome-wide resource for future genetic association studies in the Nordic countries.

European Journal of Human Genetics advance online publication, 28 July 2010; doi:10.1038/ejhg.2010.112

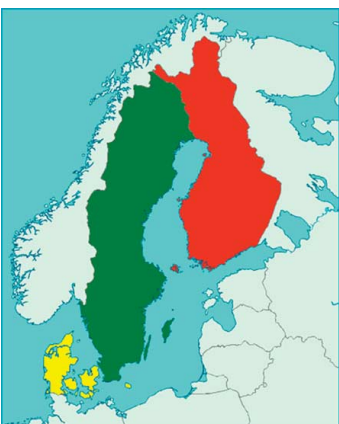
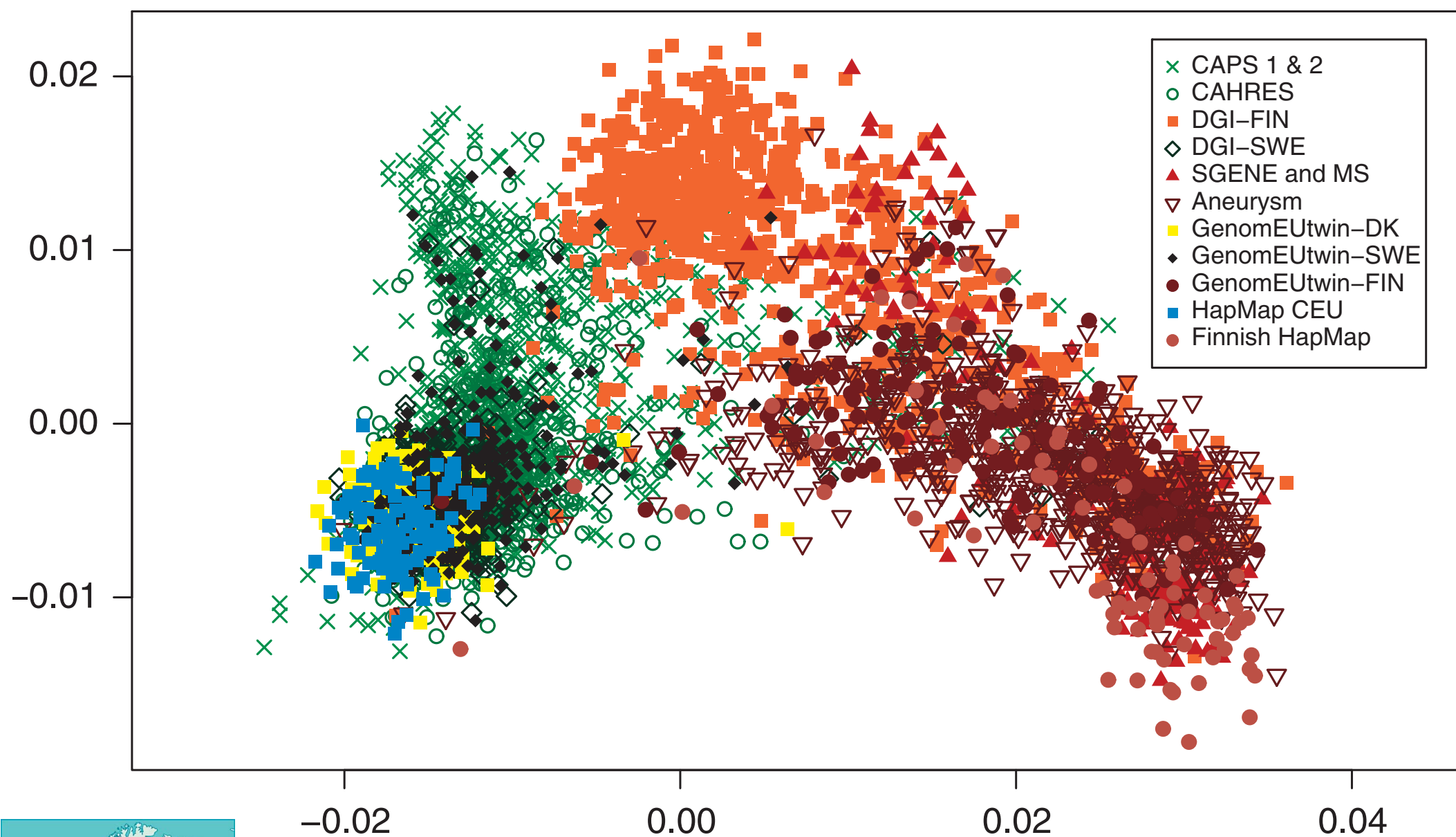


Figure 1 (a) Top axes of genetic variation in the Nordic Control Database, NordicDB (4620 samples) contrasted with the HapMap CEU (108 samples) and a Finnish HapMap reference population (81 samples). The MDS analysis was performed on $\sim 45,000$ SNPs that were common between genotyping platforms. The controls are part of the following studies: Cancer Prostate in Sweden (CAPS) 1 and 2, Cancer and Hormonal Replacement in Sweden (CAHRES), Diabetes Genetics Initiative in Western Finland and Southern Sweden (DGI-FIN and DGI-SWE), SGENE and MS in the Helsinki region, Aneurysm study in the Helsinki region, GenomEUtwin Denmark (GenomEUtwin-DK), GenomEUtwin Sweden (GenomEUtwin-SWE) and GenomEUtwin Finland (GenomEUtwin-FIN). (b) Geographical map of Scandinavia with three countries highlighted to show the origin of the samples in panel a: Finland (red), Sweden (green) and Denmark (yellow).

GWAS results: p-values

Example of GWAS results (asthma)

Manhattan plot displays all SNPs on x-axis (order by genomic location), and $-\log_{10}$ of p-values on y-axis.

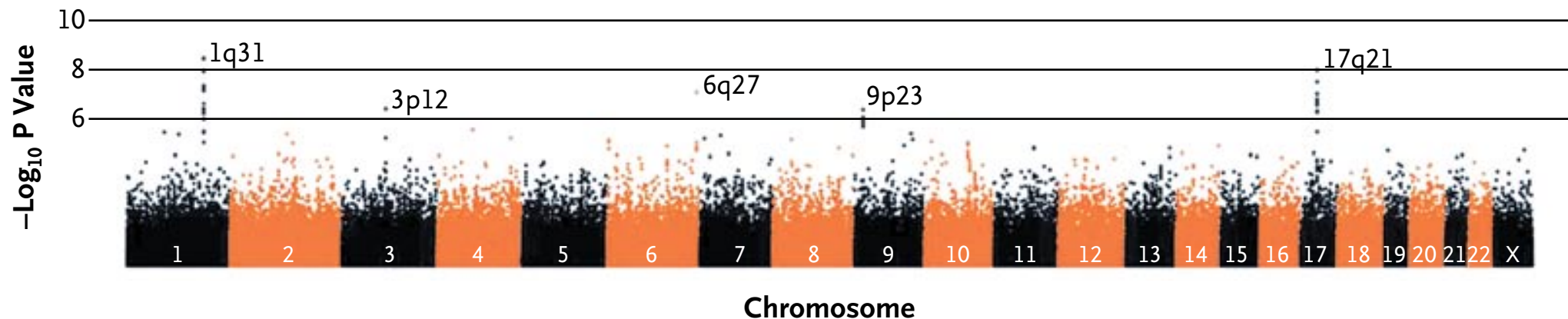


Figure 2. Manhattan Plot of the Results from the Combined Subjects of European Ancestry Who Had Asthma.

The $-\log_{10}$ P values are plotted against the physical distance. Only the two loci at chromosome 1q31 and 17q21 were significantly associated with asthma after Bonferroni correction. Individual chromosome labels are indicated in white within the Manhattan plot.

Variants of *DENND1B* Associated with Asthma in Children

Patrick M.A. Sleiman, Ph.D., James Flory, Ph.D., Marcin Imielinski, M.D., Ph.D., Jonathan P. Bradfield, B.S., Kiran Annaiah, M.Sc., Saffron A.G. Willis-Owen, Ph.D., Kai Wang, Ph.D., Nicholas M. Rafaels, M.S., Sven Michel, Ph.D., Klaus Bonnelykke, M.D., Ph.D., Haitao Zhang, Ph.D., Cecilia E. Kim, B.A., Edward C. Frackelton, B.A., Joseph T. Glessner, M.Sc., Cuiping Hou, M.Sc., F. George Otieno, M.Sc., Erin Santa, B.A., Kelly Thomas, B.A., Ryan M. Smith, B.A., Wendy R. Glaberson, B.A., Maria Garris, B.A., Rosetta M. Chiavacci, B.S.N., Terri H. Beaty, Ph.D., Ingo Ruczinski, Ph.D., Jordan M. Orange, M.D., Ph.D., Julian Allen, M.D., Jonathan M. Spergel, M.D., Ph.D., Robert Grundmeier, M.D., Ph.D., Rasika A. Mathias, Sc.D., Jason D. Christie, M.D., Erika von Mutius, M.D., William O.C. Cookson, M.D., Michael Kabesch, M.D., Miriam F. Moffatt, Ph.D., Michael M. Grunstein, M.D., Ph.D., Kathleen C. Barnes, Ph.D., Marcella Devoto, Ph.D., Mark Magnusson, M.D., Hongzhe Li, Ph.D., Struan F.A. Grant, Ph.D., Hans Bisgaard, M.D., and Hakon Hakonarson, M.D., Ph.D.

N Engl J Med 2010; 362:36-44 | [January 7, 2010](#)

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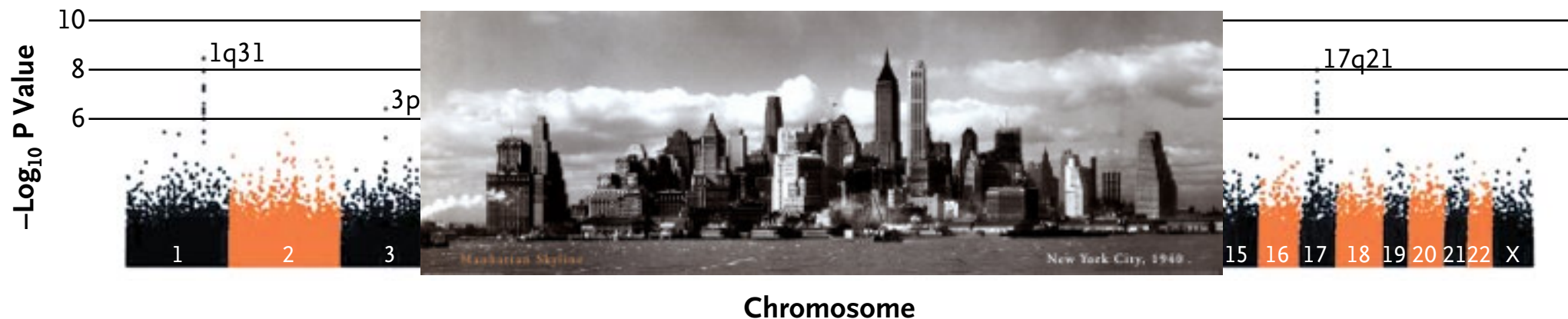


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N Engl J Med 2010; 362:36-44 | [January 7, 2010](#)

Online phenotype association resources

- NHGRI's Catalog of Published GWAS:

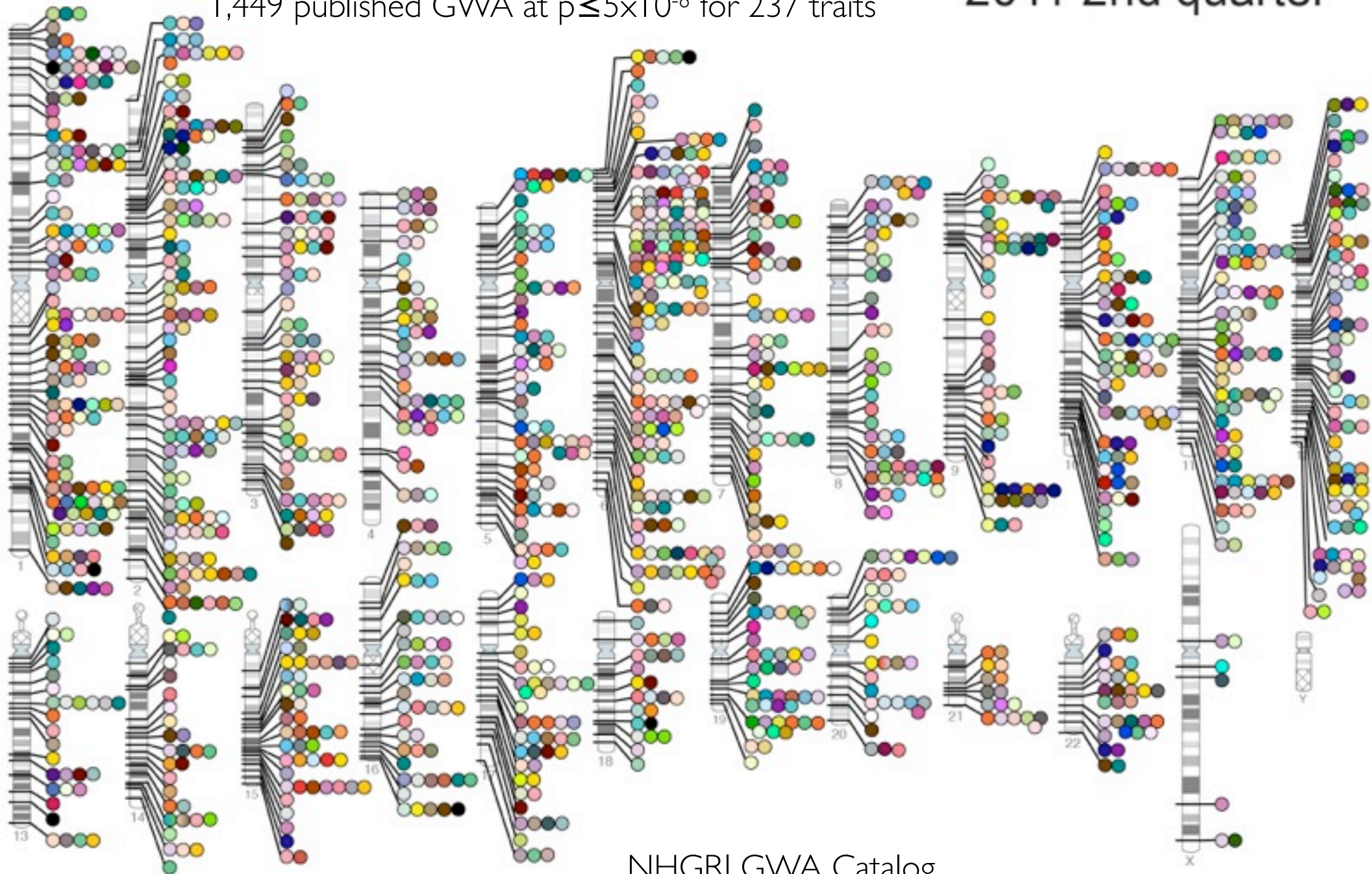
<http://www.genome.gov/GWASStudies/>

- SNPedia:

<http://www.snpedia.com>

Published Genome-Wide Associations through 06/2011,
1,449 published GWA at $p \leq 5 \times 10^{-8}$ for 237 traits

2011 2nd quarter



NHGRI GWA Catalog
www.genome.gov/GWAStudies

Abdominal aortic aneurysm	Coffee consumption	Hepatocellular carcinoma	Neuroblastoma	Response to clopidogrel therapy
Acute lymphoblastic leukemia	Cognitive function	Hirschsprung's disease	Nicotine dependence	Response to hepatitis C treat
Adhesion molecules	Conduct disorder	HIV-1 control	Obesity	Response to interferon beta therapy
Adiponectin levels	Colorectal cancer	Hodgkin's lymphoma	Open angle glaucoma	Response to metformin
Age-related macular degeneration	Corneal thickness	Homocysteine levels	Open personality	Response to statin therapy
AIDS progression	Coronary disease	Hypospadias	Optic disc parameters	Restless legs syndrome
Alcohol dependence	Creutzfeldt-Jakob disease	Idiopathic pulmonary fibrosis	Osteoarthritis	Retinal vascular caliber
Alopecia areata	Crohn's disease	IFN-related cytopeni	Osteoporosis	Rheumatoid arthritis
Alzheimer disease	Crohn's disease and celiac disease	IgA levels	Otosclerosis	Ribavirin-induced anemia
Amyloid A levels	Cutaneous nevi	IgE levels	Other metabolic traits	Schizophrenia
Amyotrophic lateral sclerosis	Cystic fibrosis severity	Inflammatory bowel disease	Ovarian cancer	Serum metabolites
Angiotensin-converting enzyme activity	Dermatitis	Insulin-like growth factors	Pancreatic cancer	Skin pigmentation
Ankylosing spondylitis	DHEA-s levels	Intracranial aneurysm	Pain	Smoking behavior
Arterial stiffness	Diabetic retinopathy	Iris color	Page's disease	Speech perception
Asparagus anosmia	Dilated cardiomyopathy	Iron status markers	Panic disorder	Sphingolipid levels
Asthma	Drug-induced liver injury	Ischemic stroke	Parkinson's disease	Statin-induced myopathy
Atherosclerosis in HIV	Drug-induced liver injury (providin-dansens)	Juvenile idiopathic arthritis	Periodontitis	Stroke
Atrial fibrillation	Endometrial cancer	Keloid	Peripheral arterial disease	Sudden cardiac arrest
Attention deficit hyperactivity disorder	Endometriosis	Kidney stones	Personality dimensions	Suicide attempts
Autism	Eosinophil count	LDL cholesterol	Phosphatidylcholine levels	Systemic lupus erythematosus
Basal cell cancer	Eosinophilic esophagitis	Leprosy	Phosphorus levels	Systemic sclerosis
Behcet's disease	Erectile dysfunction and prostate cancer treatment	Leptin receptor levels	Photic sneeze	T-tau levels
Bipolar disorder	Erythrocyte parameters	Liver enzymes	Phyosterol levels	Tau AB1-42 levels
Biliary atresia	Esophageal cancer	Longevity	Platelet count	Telomere length
Bilirubin	Essential tremor	LP (a) levels	Polycystic ovary syndrome	Testicular germ cell tumor
Bitter taste response	Exfoliation glaucoma	LpPLA(2) activity and mass	Primary biliary cirrhosis	Thyroid cancer
Birth weight	Eye color traits	Lung cancer	Primary sclerosing cholangitis	Thyroid volume
Bladder cancer	F cell distribution	Magnesium levels	PR interval	Tooth development
Bleomycin sensitivity	Fibrinogen levels	Major mood disorders	Progranulin levels	Total cholesterol
Blond or brown hair	Folate pathway vitamins	Malaria	Progressive supranuclear palsy	Triglycerides
Blood pressure	Follicular lymphoma	Male pattern baldness	Prostate cancer	Tuberculosis
Blue or green eyes	Fuch's corneal dystrophy	Mammographic density	Protein levels	Type 1 diabetes
BMI, waist circumference	Freckles and burning	Matrix metalloproteinase levels	PSA levels	Type 2 diabetes
Bone density	Gallstones	MCP-1	Psoriasis	Ulcerative colitis
Breast cancer	Gastric cancer	Melanoma	Psoriatic arthritis	Urate
C-reactive protein	Glioma	Menarche & menopause	Pulmonary funct. COPD	Urinary albumin excretion
Calcium levels	Glycemic traits	Meningococcal disease	QRS interval	Urinary metabolites
Cardiac structure/function	Hair color	Metabolic syndrome	QT interval	Uterine fibroids
Cardiovascular risk factors	Hair morphology	Migraine	Quantitative traits	Venous thromboembolism
Carnitine levels	Handedness in dyslexia	Moyamoya disease	Recombination rate	Ventricular conduction
Carotenoid/tocopherol levels	HDL cholesterol	Multiple sclerosis	Red vs. non-red hair	Vertical cup-disc ratio
Celiac disease	Heart failure	Myeloproliferative neoplasms	Refractive error	Vitamin B12 levels
Celiac disease and rheumatoid arthritis	Heart rate	Myopia (pathological)	Renal cell carcinoma	Vitamin D insufficiency
Cerebral atrophy measures	Height	N-glycan levels	Renal function	Vitiligo
Chronic lymphocytic leukemia	Hemostasis parameters	Narcolepsy	Response to antidepressants	Warfarin dose
Chronic myeloid leukemia	Hepatic steatosis	Nasopharyngeal cancer	Response to antipsychotic therapy	Weight
Cleft lip/palate	Hepatitis	Natriuretic peptide levels	Response to carbamazepine	White cell count
				White matter hyperintensity
				YKL-40 levels

Mini-exercise

Go this web-site:

NHGRI's Catalog of Published GWAS

<http://www.genome.gov/GWASudies/>

1. Look around !
2. Search by
 - Disease/Trait: **Type 2 diabetes**
 - P-value threshold: **20** ($=10^{-20}$)
3. Common top SNPs ?
4. Common genes (but different SNPs) ?

(Systematic approach: Meta-analysis, Imputation)

First Author/ Date/ Journal/ Study	Disease /Trait	Initial Sample Size	Replication Sample Size	Region	Reported Gene(s)	Strongest SNP-Risk Allele	Risk Allele Frequency in Controls	P-value	OR or beta- coefficient and [95% CI]	Platform [SNPs passing QC]
Voight June 27, 2010 <i>Nat Genet</i>	Type 2 diabetes	8,130 European descent cases, 38,987 European descent controls	Up to 34,412 European descent cases, 59,925 European descent controls	10q25.2	<i>TCF7L2</i>	rs7903146-T		2×10^{-51}	1.4 [1.34-1.46]	Affymetrix & Illumina [2,426,886] (imputed)
				11q13.4	<i>CENTD2</i>	rs1552224-A		1×10^{-22}	1.14 [1.11-1.17]	
				6p22.3	<i>CDKAL1</i>	rs10440833-A		2×10^{-22}	1.25 [1.20-1.31]	
Takeuchi April 29, 2009 <i>Diabetes</i>	Type 2 diabetes	519 Japanese cases, 503 Japanese controls	5,629 Japanese cases, 7,370 Japanese controls	9p21.3	<i>CDKN2A</i> , <i>CDKN2B</i>	rs2383208-A	0.55	2×10^{-29}	1.34 [1.27-1.41]	Illumina [482,625]
				11p15.5	<i>KCNQ1</i>	rs2237892-C	0.59	1×10^{-26}	1.33 [1.27-1.41]	
Timpson December 03, 2008 <i>Diabetes</i>	Type 2 diabetes	1,924 cases, 2,938 controls	3,757 cases, 5,346 controls	10q25.2	<i>TCF7L2</i>	rs7903146-?	NR	9×10^{-30} (non- obese)	1.49 [1.39-1.59]	Affymetrix [393,453]
Yasuda August 17, 2008 <i>Nat Genet</i>	Type 2 diabetes	187 Japanese cases, 1,504 Japanese controls	6,552 Asian cases, 6,621 Asian controls, 2,830 cases, 3,740 controls (Swedish)	11p15.5	<i>KCNQ1</i>	rs2237892-C	0.61	2×10^{-42}	1.4 [1.34-1.47]	Invader [82,343]
Zeggini March 30, 2008 <i>Nat Genet</i>	Type 2 diabetes	4,549 cases, 5,579 controls	24,194 cases, 55,598 controls	10q25.2	<i>TCF7L2</i>	rs7903146-T	NR	3×10^{-23}	1.37 [1.28-1.47]	Affymetrix and Illumina [2,202,892] (imputed)
Saxena April 26, 2007 <i>Science</i>	Type 2 diabetes	1,464 cases, 1,467 controls	5,065 cases, 5,785 controls (also includes meta-analysis from DGI +FUSION +WTCCC)	10q25.2	<i>TCF7L2</i>	rs7903146-T	0.26	2×10^{-31}	1.38 [1.31-1.46]	Affymetrix [386,731]
Zeggini April 26, 2007 <i>Science</i>	Type 2 diabetes	1,924 cases, 2,938 controls	3,757 cases, 5,346 controls (also includes meta-analysis from DGI +FUSION +WTCCC)	10q25.2	<i>TCF7L2</i>	rs7901695-C	NR	1×10^{-48} (DGI +FUSION +WTCCC)	1.37 [1.31-1.43]	Affymetrix [393,453]
Sladek February 11, 2007 <i>Nature</i>	Type 2 diabetes	661 cases, 614 controls	2,617 cases, 2,894 controls	10q25.2	<i>TCF7L2</i>	rs7903146-T	0.30	2×10^{-34}	1.65 [1.28, 2.02]	Illumina [392,935]

SNPedia

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Earwax

[rs17822931](#) determines wet vs dry earwax [[PMID 16444273](#)]

This can also be used to distinguish asian ancestry.

[NCBI coffeebreak](#) introduction

Category: [Is a medical condition](#)

[The DNA Ancestry Project](#) Discover Your Ancestry with DNA. Find Ethnic and Geographic Origins. [www.DNAAncestry](#)

[High throughput screening](#) Unknown mutations Detection BRCA1 & BRCA2 [www.fluigent.com/](#)

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- Navigenics

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Type 2 Diabetes

AS LOW AS 8 % AS HIGH AS 52 % What's your genetic risk? [see more](#)

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